REMARKS

Amendments

Upon entry of this amendment, claims 1, 2, 6, 7, 9, 10-12, 60 and 80-83 will be pending. Claims 3-5, 8, 13-59 and 61-79 have been canceled, without prejudice or disclaim. Claims 1, 2, 6, 7, 9, 10 and 60 have been amended, and new claims 80-83 have been added. Support for the amendments to claim 1 can be found in the originally filed specification at, *e.g.*, page 6, lines 4-6; page 8, lines 20-22; and in original claim 5. Support for the amendments to claim 2 can be found in original claims 3 and 4. Support for amendments to claims 6 and 7 can be found throughout the originally filed specification. Support for the amendments to claim 9 can be found in the originally filed specification at, *e.g.*, page 6, lines 9-11; and in original claim 5. Support for amendment to claim 10 can be found throughout the originally filed specification. Support for the amendments to claim 60 can be found in original claims 5 and 58. Support for new claims 80-82 can be found in the specification at, *e.g.*, page 10, lines 1-10; and in original claims 1 and 5. Support for new claim 83 can be found in the specification at, *e.g.*, page 6, lines 9-11; and in original claim 60. No new matter has been added.

Restriction Requirement

The Examiner has acknowledged that Applicants have elected Group I, containing claims 1-7, 9-12, and 60. Applicants note that the claims read upon the species of schizophrenia as the neurological disorder, as indicated in paragraph 4 of the Office Action, not Alzheimer's Disease, as indicated in paragraph 11 of the Office Action.

Information Disclosure Statements

Applicants note with appreciation that the Examiner has indicated that the references cited in the Information Disclosure Statements filed by Applicants on November 16, 2004 and August 25, 2005 have been considered by the Examiner.

Specification

The Examiner has indicated that the specification is objected to because the title of the invention is not descriptive. The title has been amended herein to recite "USE OF SLURP-1 COMPOSITIONS FOR TREATING SCHIZOPHRENIA." Thus, this objection has been overcome and should be withdrawn.

Claim objections

Claim 5 is objected to for encompassing non-elected inventions. Claim 5 is canceled herein. Therefore, this objection is moot and should be withdrawn.

Claim 60 is objected to for depending from claim 58, which is withdrawn. Claim 58 is canceled herein, and claim 60 has been amended herein to be in independent form. Thus, this objection has been overcome and should be withdrawn.

Claim rejections

35 U.S.C. § 112, first paragraph

Enablement

Claims 1-7, 9-12 and 60 have been rejected under 35 USC § 112, first paragraph for lack of enablement. Claims 3-5 have been canceled herein. Therefore, this rejection is moot in regard to these claims. The Examiner states that the remaining claims are not enabled because the instant specification fails to teach how to achieve the proposed treatment, thereby requiring undue experimentation for one skilled in the art to used the claimed invention with a reasonable expectation of success. (Office Action at page 4.) To support this rejection, the Examiner has applied the factors described in *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

This rejection is traversed for at least the following reasons.

As a preliminary matter, Applicants not that the pending claims have been amended herein to specify the treatment of a specific neurological disorder, namely schizophrenia. Thus, the Examiner's statements regarding retreatment of "any 'neurological disorder'" are no longer applicable to the pending claims, as amended herein. Accordingly, the enablement rejection is addressed herein to the extent it applies to treatment of schizophrenia by SLURP-1 polypeptide compositions.

The Examiner acknowledges that the present specification teaches that SLURP-1 is useful in the treatment and/or prevention of a pathology caused by dysfunction of an acetylcholine receptor, including neurological disorders such as schizophrenia. (Office Action at page 5.) Moreover, the Examiner also states that it has been established that the alpha7 nicotinic acetylcholine receptor is an important mediator in epidermal homeostasis and inflammation, and that mutations in SLURP-1, which has been demonstrated to modulate the activity of the alpha7 nicotinic acetylcholine receptor, have been implicated in the neurological disorder Mal de Meleda. (Id.) However, the Examiner asserts that no nexus exists between a SLURP-1 protein and any neurological disorder to be treated, such that one skilled in the art would not expect that the administration of a SLURP-1 protein would result in treatment of schizophrenia. (Id.)

In response, Applicants submit that there is a clear nexus between a SLURP-1 protein and the treatment of schizophrenia because the alpha7 nicotinic acetylcholine receptor is a well-recognized target for treatment of schizophrenia. For example, agonists of the alpha7 nicotinic acetylcholine receptor have previously been proposed as drugs for the treatment of schizophrenia. (*See*, e.g., Martin *et al.* (2004) "Alpha-7 nicotinic acetylcholine receptor agonists: potential new candidates for the treatment of schizophrenia," Psychopharmacology 174:54-64, herein "Martin", courtesy copy enclosed.) Here, for the first time, Applicants have demonstrated that SLURP-1 is an agonist of the alpha7 nicotinic acetylcholine receptor (*See*, *e.g.*, Examples 4 and 5 of the instant application). Because, as noted, the Alpha-7 nicotinic acetylcholine receptor is a well recognized target for treatment of schizophrenia, Applicants assert that one of skill in the art would reasonably expect that the administration of a SLURP-1 protein would have a beneficial effect in the treatment of schizophrenia.

The Examiner also indicates that the specification fails to disclose whether or not an administered SLURP-1 protein would cross the blood-brain barrier ("BBB") in order to reach the target cells at a concentration sufficient for treatment. (Office Action at pages 5-6.) Moreover, the Examiner also asserts that the ability of therapeutic compounds to cross the BBB is a major obstacle to this type of therapy, and cites Miller (2002) Science 297:1116-1118, (herein "Miller") to support this position.

However, Applicants note that Miller teaches that "[a]s a general rule...only lipophilic molecules smaller than about 500 Daltons can cross from blood to brain." For that reason, pharmaceutical companies have turned their attention to small molecules to develop treatments

for disorders of the central nervous system, including schizophrenia. (*See,* Miller at page 1116, columns 2 and 3.) Nevertheless, it is recognized in the art that the BBB is perturbed in some schizophrenia patients. (*See, e.g.*, Kirch *et al.* (1985) "Abnormal cerebrospinal fluid protein indices in schizophrenia," Bio. Psychiatry 20:1039-46, herein "Kirch I", courtesy copy enclosed; and Kirch *et al.* (1992) "Blood-CSF barrier permeability and central nervous system immunoglobulin G in schizophrenia," J. Neural Transm. 89:219-232, herein "Kirch II", courtesy copy enclosed; and references cited therein.) Kirch I teaches that, in one group of schizophrenia patients, permeability of the BBB was increased relative to normal subjects without CSF abnormalities, as demonstrated by elevated serum albumin levels in the CSF. (*See,* Kirch I, pages 1041-43 and Figure 1.) In addition, Kirch I also teaches that in a separate group of schizophrenia patients, permeability of the BBB was increased relative to normal subjects without CSF abnormalities, as demonstrated by elevated serum immunoglobulin levels in the CSF. (*See,* Kirch I, pages 1041-43 and Figure 2.) These results were replicated in a later study, which demonstrated that the increased serum albumin and immunoglobulin levels in groups of schizophrenics were not the result of the treatment of the subjects with neuroleptics. (*See,* Kirch II, pages 224-225.)

Thus, Applicants submit that the teachings of Kirch I and Kirch II demonstrate that the BBB is perturbed in schizophrenics such that serum albumin, having a molecular weight of 66 kDa, and serum immunoglobulin, having a molecular weight of 150 kDa, are able to cross the BBB. The present application discloses a SLURP-1 protein having 103 amino acids (corresponding to an isotopically averaged weight of 11185 Daltons). Moreover, a mature form of the SLURP-1 protein that contains amino acids 23-103, has an isotopically averaged weight of 8853 Daltons. (*See* the specification at page 6; molecular weight calculations performed using Protein Calculator v3.3, available at http://www.scripps.edu/~cdputnam/protcalc.html.) Thus, in view of the teachings of Kirch I and Kirch II, Applicants contend that one of skill in the art would anticipate that the SLURP-1 polypeptides disclosed in the present application would be able to cross the BBB in schizophrenic subjects.

The Examiner also states that, even if a nexus between the SLURP-1 polypeptide and the pathogenesis of schizophrenia was established, in view of the lack of working examples, one skilled in the art would have to perform an undue amount of experimentation to use the claimed methods to treat schizophrenia or any "neurological disorder." (Office Action at page 7.) In

response, even in the absence of working examples in the specification relating to the treatment of schizophrenia using a SLURP-1 polypeptide of the invention, based on the combined teachings of the instant application and the prior art, one skilled in the art would be able to make and use the claimed invention without undue experimentation. For each of these reasons, Applicants contend that pending claims 1, 2, 6, 7, 9-12 and 60 are enabled by the specification. Thus, this rejection should be withdrawn.

35 U.S.C. § 112, second paragraph

Claims 1-7, 9-12 and 60 have been rejected under 35 USC § 112, second paragraph as indefinite. Claims 3-5 have been canceled herein. Therefore, this rejection is moot in regard to these claims. The Examiner contends that the remaining claims are indefinite because the mere recitation of the name "SLURP-1" is not sufficient to satisfy the requirement of adequately describing and setting forth the inventive concept. (Office Action at page 8.) As suggested by the Examiner, Applicants have amended claim 1 herein to recite, in relevant part, "a SLURP-1 polypeptide comprising the amino acid sequence of SEQ ID NO: 2." Claim 9 has also been amended herein to recite, in relevant part, "a SLURP-1 polypeptide comprising amino acids 23-103 of the amino acid sequence of SEQ ID NO: 2." Likewise, claim 60 has been amended herein to recite, in relevant part, "a peptide mimetic of the SLURP-1 polypeptide of SEQ ID NO: 2." Therefore, Applicants assert that independent claims 1, 9 and 60 as amended herein are adequately described and meet the requirements of 35 U.S.C. § 112, second paragraph. Claims 2, 6, 7, and 10-12 each depend (directly or indirectly) from claim 1 or 9 and, as such, contain all the limitations thereof. Thus, Applicants submit that these claims are also adequately described and meet the requirements of 35 U.S.C. § 112, second paragraph. Moreover, new independent claim 80 recites, in relevant part, "a SLURP-1 polypeptide at least 90% identical to the amino acid sequence of SEQ ID NO: 2." Thus, Applicants assert that new claim 80, as well as new claims 81-82, which depend therefrom, are also definite.

The Examiner has also rejected claims 1-7, 9-12 and 60 under 35 USC § 112, second paragraph as indefinite because the claims do not have a step that clearly relates back to the preamble. Claims 3-5 have been canceled herein. Therefore, this rejection is moot in regard to these claims. Moreover, claims 1, 9 and 60 have been amended herein to specify the result of treating schizophrenia in the subject. Thus, Applicant submits that these claims, as amended

herein relate back to the preamble. Thus, this rejection has been overcome and should be withdrawn. Likewise, the remaining claims each depend from claim 1, 9 or 60 (directly or indirectly) and therefore contain all the limitations of these claims. As such, these claims also meet the requirements of 35 U.S.C. § 112, second paragraph. Further, newly added claim 80 specifies the result of treating schizophrenia in the subject. Thus, new claim 80, and dependent claims 81 and 82 also meet the requirements of 35 U.S.C. § 112, second paragraph.

CONCLUSION

On the basis of the foregoing amendments, Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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